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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,570	09/04/2003	Danny Allen	MUR-005	6430

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EXAMINER	
ASHEN, JON BENJAMIN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/655,570	ALLEN ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,18,20,23,24,26,28 and 31* is/are pending in the application.

4a) Of the above claim(s) *23,24,26 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,18,20 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

1. Claims 1, 18, 20, 23-24, 26, 28 and 31 are pending in this application. Claims 2-17, 19, 21-22, 27, 27 and 29-30 have been cancelled by Applicant. Claim 1 is currently amended. Claims 23, 24, 26 and 31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1, 18, 20 and 28 are currently under examination.

Applicant's response filed 12/14/2005 has been fully considered. Rejections and/or objections not reiterated from the previous office action mailed 08/14/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

2. The amendment filed 12/14/2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Section [0042] has been amended to state that, "The constructs may also optionally include additional cleaving elements(s)" which changes the scope of the disclosure and is therefore considered to constitute the addition of new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

3. Claims 1, 18, 20 and 28 remain rejected under 35 U.S.C. 112, second paragraph for the reasons of record as set forth in the Action mailed 08/12/2005.

Additionally, claim 1 as amended now recites, "further comprising a cleaving element capable of cleaving the nucleotide sequence 5' and/or 3' to the RNAi." However, the skilled artisan cannot determine the metes and bounds of what is being claimed with this terminology, without assumption, because it is not clear how a cleaving element can be capable of cleaving a nucleotide sequence that is located 5' and/or 3' to "the RNAi" which, as known and used in the art, is a process or activity, not a compound or composition (see also below).

Moreover, the terminology, "further comprising a cleaving element capable of cleaving the nucleotide sequence 5' and/or 3' to the RNAi" renders the claim indefinite because "the nucleotide sequence" refers back to a nucleotide sequence encoding an RNAi. However, it is not clear how "the nucleotide sequence that is 5' and/or 3' to the RNAi" could be cleaved by a cleaving element because there is no nucleotide sequence 5' and or 3' to the RNAi. The only nucleotide sequence present in the claim is the nucleotide sequence that encodes the RNAi an once this is transcribed the RNAi has only the sequence of itself, as claimed.

Therefore the skilled artisan cannot determine the metes and bounds of what is being claimed without assumption.

Response to Arguments- Claim Rejections - 35 USC § 112

4. Applicant's arguments filed 12/14/2005 have been fully considered but they are not persuasive. Applicant has "acknowledged" that the acronym RNAi has more that one definition in the art , for example "RNA interference" refers to the process and "interfering RNA" refers to the compound. However, it is not clear what applicant is acknowledging, because the outstanding grounds of rejection considers that the acronym RNAi refers to the process and that the term RNAi does not have more than one definition in the art. Applicant was encouraged, in the Action mailed 08/12/2005, to indicate where support in the art or the instant specification for RNAi as a compound could be located and to cite this art in their response (see pg. 3, Action mailed 8/12/05). Applicant has not cited any support in the art for RNAi as a compound and has pointed to paragraph 3 of the specification as providing a definition of RNAi as pertaining to "interfering RNA." Applicant has then argued that depending on the context in the specification and claims, RNAi could have either definition which would be readily recognized by one of skill. However, paragraph 3 of the specification as filed provides no limiting definition of "RNAi" but states that a new tool for modulating or suppressing gene expression has been described called "interfering RNA" which is abbreviated as "(RNAi)." Absent a definition of the term "RNAi" in the specification, such that applicant could rely upon that definition where it is different from the known and used meaning of "RNAi' in the art, which is that of a process not a compound, the instant claims remain indefinite because the skilled artisan cannot determine the metes and bounds of what is

being claimed, without assumption, wherein a nucleotide sequence encodes a process, for example.

5. Claims 1, 18, 20 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the limitation "the nucleotide sequence" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claim 20 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. In the instant case, A host cell comprising the polynucleotide according to claim 1 reads on a transgenic human, which is non-statutory subject matter. Amendment to recite, "An isolated host cell..." would be remedial.

Claim Rejections - 35 USC § 102-withdrawn

8. The rejections of claims 1, 18, 20 and 28 under 35 U.S.C. § 102(e) as being anticipated by Yu et al., under 35 U.S.C. 102(e) as being anticipated by Engelke et al. (US 2003/0148519) and Graham (US 6,573,099 B2) and the rejection of claims 1 and 28 under 35 U.S.C. 102(e) as being anticipated by Fire et al. (US 6,506,559 B1), are

withdrawn in view of Applicant's amendment of instant claim 1 to recite a limitation not disclosed in the cited references.

Claim Rejections - 35 USC § 102-New (necessitated by Amendment)

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1, 18, 20, and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Waterhouse et al (US 6,423,885).

In light of the 112 2nd rejection set forth above, a reasonable interpretation of what is being claimed considers that an RNA transcript that encodes "an RNAi" , considered a compound, also encodes a cleaving element that is a ribozyme that is capable of auto-catalytically cleaving the transcript that encodes it and will therefore, inherently cleave either 5' or 3' or both of the "RNAi." The following prior art is applied.

The instant invention is drawn to a polynucleotide comprising a nucleotide sequence encoding an RNAi operatively linked to a tissue specific promoter, a cell specific promoter, and/or an inducible promoter further comprising a cleaving element capable of cleaving the nucleotide sequence 5' and/or 3' to the RNAi. The invention is

further drawn to a vector, host cell, or pharmaceutical composition comprising the polynucleotide, wherein the pharmaceutical composition further comprises an excipient.

Waterhouse et al. disclose polynucleotide constructs that are DNA vectors that express double stranded RNAs that mediate co-suppression (also known as post transcriptional gene silencing or RNA interference and therefore reasonably considered to be "an RNAi") in plants (col. 1, cols. 9-11). The polynucleotide constructs of disclosed by Waterhouse et al. are chimeric DNAs which when transcribed under control of conventional promoter and 3' end formation and polyadenylation regions yield RNA molecules wherein at least the polyadenylation signal may be removed by the autocatalytic activity of a self-splicing ribozyme comprised within the transcribed RNA molecules. The autocatalytic self-splicing ribozyme is reasonably considered a cleaving element. Waterhouse et al. also disclose plants and plant cells comprising RNA molecules as above or chimeric DNA encoding RNA molecules as above and that similar methods and means for reducing the phenotypic expression of a nucleic acid by co-suppression in eukaryotic cells are provided (col. 1, lines 5-20; col. 2, line 60 bridge to col. 3, line 8). Waterhouse et al. disclose that the promoter is a tissue specific, inducible or constitutive promoter (col. 3). Waterhouse et al. disclose that another objective of the invention is to provide a method for reducing the phenotypic expression of a nucleic acid of interest, which is normally capable of being expressed in a eukaryotic cell, the method comprising the step of providing to the nucleus of said eukaryotic cell aberrant RNA of the invention as above, which is considered an inherent disclosure of a pharmaceutical composition. This consideration is based on the

inherent composition, although not specifically recited in the cited reference, of the above chimeric DNA constructs, in water, or some other pharmaceutical excipient for delivery to cells.

Therefore, Waterhouse et al. anticipate the instant invention as set forth in claims 1, 18, 20 and 28.

Claim Rejections - 35 USC § 103-New (necessitated by Amendment)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 18, 20 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waterhouse et al. as applied to claims 1, 18, 20 and 28 above, and further in view of Elbashir et al (of record).

The instant invention is drawn to a polynucleotide comprising a nucleotide sequence encoding an RNAi operatively linked to a tissue specific promoter, a cell specific promoter, and/or an inducible promoter further comprising a cleaving element capable of cleaving the nucleotide sequence 5' and/or 3' to the RNAi. The invention is further drawn to a vector, host cell, or pharmaceutical composition comprising the polynucleotide, wherein the pharmaceutical composition further comprises an excipient.

The teachings of Waterhouse et al. are relied upon as above. In particular, in light of the 112 2nd rejection set forth above, the disclosure of Waterhouse et al. of a

self-splicing ribozyme comprised within the transcribed RNA molecules is reasonably considered to be an embodiment of a cleaving element that falls within the scope of what is claimed. Waterhouse et al. do not provide an explicit disclosure of a pharmaceutical composition comprising the claimed polynucleotide.

Elbashir et al. teach that siRNA duplexes mediate RNA interference in cultured mammalian cells and that siRNAs are extraordinarily powerful reagents for mediating gene silencing , effective at concentrations that are several orders of magnitude lower than concentrations applied for conventional antisense or ribozyme gene targeting experiments (pg. 496, col. 1). Elbashir et al. teach that RNAi is a process of sequence-specific gene silencing initiated by dsRNA that is homologous in sequence to the silenced gene and disclose that the structure of effective siRNAs are double stranded RNAs that comprise sense and antisense RNA strands of 21 nucleotides in length that are complementary over 19 base pairs. Elbashir et al. teach transfection of mammalian cells in culture using siRNAs comprised in liposomes, considered here to be an inherent teaching of a pharmaceutical composition (pg. 497, col. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the instant invention was made, to make an siRNA to inhibit the expression of a target gene (as taught by Elbashir et al.) wherein the siRNA was expressed from a DNA construct that comprised a nucleotide sequence operatively linked to a promoter that was a tissue specific or constitutive or inducible promoter and that further comprised a self-splicing ribozyme wherein the construct was comprised in a vector that was comprised in a cell and a pharmaceutical composition comprising the above construct

(as taught by Waterhouse et al.) in order to express an siRNA in a cell to mediate effective gene silencing (as taught by Elbashir et al.).

One of ordinary skill in the art would have been motivated to make an siRNA to inhibit the expression of a target gene (as taught by Elbashir et al.) wherein the siRNA was expressed from a DNA construct that comprised a nucleotide sequence operatively linked to a promoter that was a tissue specific or constitutive or inducible promoter and that further comprised a self-splicing ribozyme wherein the construct was comprised in a vector that was comprised in a cell and a pharmaceutical composition comprising the above construct (as taught by Waterhouse et al.) because siRNAs are extraordinarily powerful reagents for mediating gene silencing and were known to be effective at concentrations that are several orders of magnitude lower than concentrations applied for conventional antisense or ribozyme gene targeting experiments (as taught by Elbashir et al.).

One of ordinary skill in the art would have expected success in making an siRNA to inhibit the expression of a target gene (as taught by Elbashir et al.) wherein the siRNA was expressed from a DNA construct that comprised a nucleotide sequence operatively linked to a promoter that was a tissue specific or constitutive or inducible promoter and that further comprised a self-splicing ribozyme wherein the construct was comprised in a vector that was comprised in a cell and a pharmaceutical composition comprising the above construct (as taught by Waterhouse et al.) because siRNAs and pharmaceutical compositions thereof were known and used effectively in cells to mediate gene silencing (as taught by Elbashir et al.), were known to be effective at

concentrations that are several orders of magnitude lower than concentrations applied for conventional antisense or ribozyme gene targeting experiments (as taught by Elbashir et al.) and because DNA construct that comprised a nucleotide sequence operatively linked to a promoter that was a tissue specific or constitutive or inducible promoter and that further comprised a self-splicing ribozyme were known and used in the art of co-suppression (as taught by Waterhouse et al.).

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

12. No claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jba

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER